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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/955,572 10/22/97 KWON

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EXAMINER

HM12/0824

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ART UNIT

PAPER NUMBER

1646

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29

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/955,572

Applicant(s)

KWON, BYOUNG S.

Examiner

Claire M. Kaufman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- 1) ☒ Responsive to communication(s) filed on 26 April 1999.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5,6,24 and 26-31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5,6,24 and 26-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some * c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
2. ☐ received in Application No. (Series Code / Serial Number) _____.
3. ☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 14) ☒ Notice of References Cited (PTO-892)
- 15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 25
- 17) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 18) ☐ Notice of Informal Patent Application (PTO-152)
- 19) ☒ Other: *Notice to Comply*.

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DETAILED ACTION

The amendment filed April 26, 1999 has been entered.

Response to Arguments

5 Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed April 26, 1999 have been fully considered but they are not persuasive.

Sequences

10 This application contains sequence disclosures that are encompassed by the definitions for nucleic and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth in the attached Notice to Comply with Requirements for Patent Applications Containing Nucleic Sequence and/or Amino Acid Sequence Disclosures. According to the
15 updated rules for sequence compliance, sequences with more than 4 amino acids with at least four amino acids specifically identified must be represented by a unique sequence identifier in the CRF and paper copy of the Sequence Listing and be referred to by the identifier in the specification. The sequence on page 11, bridging lines 3-4, does not comply.

Claim Rejections - 35 USC § 112

20 The following is a quotation of the first paragraph of 35 U.S.C. 112:

25 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 26 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

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art to which it pertains, or with which it is most nearly connected, to use the invention for the reasons of record set forth in the previous Office action (paper #13) and as repeated below.

No guidance or examples pertaining to the use of a H4-1BB polypeptide have been disclosed that would provide a reasonable expectation of success using the claimed invention to treat a disease or clinical condition. The specification says merely that H4-1BB is expected to act like 4-1BB, which "helped B cells with proliferation" (p. 17, lines 1-4). Further, the use of H4-1BB is unpredictable because, as the specification says on p. 17, lines 4-5, the derivative H41-BB-AP can be used to suppress or enhance human immune responses. No guidance or examples are provided to enable one skilled in the art to use the claimed protein to ameliorate a condition by, for example, suppressing an immune response. Nor is it disclosed how to select enhancing *versus* suppressing activity. On page 18, lines 6-7, it is stated that H4-1BB-AP can be used for the treatment of certain autoimmune diseases. Specific diseases are not listed and it would require undue experimentation to determine which autoimmune disease(s) could be treated with H4-1BB or a portion thereof. For these reasons and because no dosage or information on toxicity, stability, half-life, or solubility of H4-1BB or fragments thereof were available at the time the invention was made, it would require undue experimentation to use the claimed invention.

Applicant argues that a pharmaceutical composition comprising a soluble H4-1BB polypeptide which comprises the extracellular domain of SEQ ID NO:2 or fragment thereof will suppress T cell-dependent immune responses as described on pages 17-18 of the specification. First, Figures 5a-c described on pages 17-18 show a schematic of cells in which the normal interaction between 4-1BB and its ligand are blocked. No experiments are presented, and basis for the effect of blocking 4-1BB is hypothetical and based on the interaction of CD28 to its counter-receptor B7. Applicant's arguments (page 6, second paragraph) are based on the knowledge that 4-1BB is transcribed during T cell activation. Induction of transcription does not necessarily lead to T cell-dependent immune responses. Also, data and hypotheses are based on

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information about murine instead of human 4-1BB, and there is evidence in the art to suggest that 4-1BB from different species behave differently (see binding characteristics described by Loo et al., X, J. Biol. Chem., 1997, on page 6452, last sentence, and Figure 6; and species different for CD2, p. 6455, col. 1). Second, for the reasons of record, there is a lack of enablement of a pharmaceutical because it carries the requirement of being enabled for treatment. The current application does not provide a reasonable expectation that the claimed composition could be used to treat due to the absence of guidance and information presented in the specification and prior art. It is suggested that if claims to a composition are desired, a claim such as "a composition comprising the polypeptide of claim 24 and a suitable diluent", would not raise the points currently at issue for a pharmaceutical composition.

The argument that one would be capable of determining whether a disease is associated with a T cell, is not persuasive. The pharmaceutical composition is not enabled for the reasons of record and as rephrased here, namely there is a lack of guidance about and examples of which disease(s) associated with T cells can be treated by affecting H4-1BB, there is a lack of predictability (see above), and it would require undue experimentation to identify a representative number of diseases/conditions which the claimed pharmaceutical could be used to treat. Without enablement for suppression of T cells, there cannot be enablement for treatment of a disease in which such suppression is required. Even though 4-1BB is transcribed during T cell activation, induction of transcription does not necessarily lead to T cell-dependent immune responses. Additionally, Loo et al. (U, J. Biol. Chem., 1997, especially p. 6455, sentence bridging col. 1-2) show that data from mouse (*e.g.*, transcription information) is not necessarily predictive of human responses. There are no examples of the ECD portion of human 4-1BB being used to treat anything in the instant application or prior art. The current application does not provide a reasonable expectation that the claimed composition could be used to treat due to the absence of guidance and information presented in the specification and prior art.

Applicant argue that the pharmaceutical composition is enabled for effective treatment of T cell-mediated immune responses because 1) the data of Linsely et al. (Science, 1992) show that B7 bound CD28 and CTLA-4, and a CTLA-4 ECD-Ig fusion suppressed T cell-dependent

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antibody response *in vivo* in mice, 2) anti-CD45R monoclonal antibodies have been shown to be effective in animal models in reversing transplant rejection, and 3) 4-1BB production is induced during T-cell activation. The argument has been fully considered, but is not persuasive. No experiments are presented, and basis for the effect of blocking 4-1BB is hypothetical and based on the interaction of CD28 to its counter-receptor B7. Applicant's arguments are based on the knowledge that 4-1BB is transcribed during T cell activation. Induction of transcription does not necessarily lead to T cell-dependent immune responses. The basis of the activity of H4-1BB cannot be based on the activity of materially distinct molecules (*e.g.*, B7) that do not themselves bind or directly interact H4-1BB. For the reasons of record, there is a lack of enablement of a pharmaceutical because it carries the requirement of being enabled for treatment. The current application does not provide a reasonable expectation that the claimed composition could be used to treat due to the absence of guidance and information presented in the specification and prior art." Additionally, in light of Loo et al. described in the preceding paragraphs, data from mouse is not necessarily predictive of human responses.

Applicants argue that selection of dosages and preparation of pharmaceutical formulations is well within the skill of the art. The argument has been fully considered, but is not persuasive. Applicants statement is correct if one reasonably expects that the active agent of the pharmaceutical preparation could be used successfully to treat a specific disease. That is not the case here. It is not known how H4-1BB effects T cells or what T cell-associated disease(s) are dependent on H4-1BB activity. The effect of a soluble H4-1BB is unpredictable based on the lack of information about human 4-1BB in the specification and showings in the prior art that suggest that murine 4-1BB acts differently than H4-1BB (*e.g.*, Loo et al.). Applicants have provided an invitation to experiment without a reasonable expectation of successful treatment of a disease. For these reasons and those set forth in the rejection above, it would require undue experimentation to use the claimed invention.

Claim Rejections - 35 USC § 112

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Claims 5, 24, 26-30 and dependent claim 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5 Claims 5, 24 and 26-30 are indefinite because it is unclear what the metes and bounds of the claims are since it is not clear from the claims or specification what besides a fragment of SEQ ID NO:2 must be present in an H4-1BB receptor protein or soluble polypeptide. For claim 24 it is unclear if a fragment of an ECD which is not part of SEQ ID NO:2 is included (see below).

10 Claims 24 and 27 are indefinite because it is unclear if the fragment is a fragment of the extracellular domain (ECD) or of SEQ ID NO:2.

Claim 28 and 30 are indefinite because it is not clear under what conditions hybridization may occur. It is unclear if the term is meant to include both specific and non-specific hybridization conditions. If conditions favoring specific hybridization are intended, it is not clear what range of conditions may be applied to meet the claim's intended scope. As a result,
15 the metes and bounds of the claim are not clear.

Oath/Declaration

The Declaration filed on March 2, 1999 under 37 CFR 1.131 has been considered but is ineffective to overcome the Schwarz et al. reference for the reasons of record set forth in the
20 previous Advisory Actions (paper numbers 21 and 18) and as repeated below.

The evidence submitted is insufficient to establish conception of the invention prior to the effective date of the Schwarz et al. reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. See
25 *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Exhibit A of the Declaration shows a portion of a specification to which the instant application claims priority. That specification suggests a method of isolating a human 4-1BB, however, no isolation was accomplished. The Declaration is insufficient because there is an insufficient showing of

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conception. Conception in this case would require actual reduction to practice: a showing that the inventor conceived of at least as much as the reference showed. The reference shows the protein extracellular domain, as it is comprised by the full-length protein, and nucleic acid sequence. In *Amgen Inc v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ2d, 1016 (CAFC 1991),
5 it was decided that for complex products, such as nucleic acids, conception is not achieved until reduction to practice is accomplished. The court stated that:

A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See *Oka*, 849
10 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more
15 specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.

20 In the instant situation, Applicant could not envision the detailed constitution (i.e. the sequence) of the extracellular domain coding region nor did Applicant have the nucleic acid encoding the extracellular domain (sequenced or not) in hand prior to Schwartz et al.

Exhibit B shows only a portion of the human 4-1BB, absent evidence to the contrary. The reason is that while the amplification primers were complementary to nucleotide sequences
25 in the extracellular domain (emphasis added by Applicant in the response) of mouse 4-1BB, there is no evidence that the primers were positioned to provide amplification of the full extracellular domain of H4-1BB. The primers referred to in the specification (paragraph bridging pages 14-15) amplify a region encoding approximately amino acids 36-58 and 116-128, not the full-length extracellular domain (see Figure 1A). Further, neither the specification nor
30 prior art teaches how to use such small fragments of the ECD of H4-1BB. Primers that one skilled in the art would reasonably expect to be able to be used successfully to amplify at least the full-length ECD are not disclosed in the Declaration.

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Applicant's assertion that Exhibit C is a Southern blot in the response is contrary to the description in the Declaration. In the Declaration, Exhibit C is described as an autoradiogram of hybridizing host cells comprising a vector with the amplified H4-1BB encoding fragment. Still, the H4-1BB cDNA is not the full-length extracellular domain encoding nucleic acid.

5 In the instant situation, Applicant could not envision the detailed constitution (*i.e.* the sequence) of the extracellular domain amino acid sequence or coding region, nor did Applicant have the nucleic acid encoding the extracellular domain (sequenced or not) in hand prior to Schwarz et al. or Goodwin et al. or Alderson et al. as applied below.

10 ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

15 A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

20 (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 5, 24, 26-28 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Goodwin et al. (B, US Patent 5, 674,704).

25 Goodwin et al. teaches the extracellular domain (ECD) of human 4-1BB. The soluble H4-1BB was expressed as a fusion protein produced by the expression of a vector comprising DNA encoding soluble human 4-1BB and an antibody Fc region (col. 20, lines 32, through col. 21, line 11). The fusion protein is also taught in a pharmaceutical composition comprising medium containing nonfat dry milk, which is a suitable diluent (col. 23, lines 57-60). It is noted
30 that because of the indefiniteness of the term "H4-1BB" as to what structural requirements the term carries, and the use of the term "comprising" in the claims, fusion proteins comprising the ECD of H4-1BB are encompassed.

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Claims 5, 24, 26-31 are rejected under 35 U.S.C. 102(a) as being anticipated by Alderson et al. (DH, Eur. J. Immunol, 1994, 24:2219-2227).

Alderson et al. teach a soluble H4-1BB polypeptide produced by transfecting a CD-1/EBNA host cell with the expression vector pDC406 containing the entire extracellular domain of H4-1BB, which is a fragment of SEQ ID NO:2 of the instant application, and purifying the protein from culture on a G-Sepharose column (p. 2220, second paragraph). The ECD was produced fused to the Fc region of human IgG1. The entire ECD is from amino acid 1-186 of Figure 1 of Alderson et al, which is identical to the same region of SEQ ID NO:2 of the instant application. Necessarily the DNA encoding this sequence would hybridize to one or more of SEQ ID NO:3-8 of the instant application as these are primers that hybridize to the naturally encoding sequence (see pages 15-16 of the instant application). Also taught is the H4-1BB ECD fusion protein in Freund's adjuvant, a pharmaceutically acceptable carrier.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 5, 24, 26-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwarz et al. (V, GenBank CD-ROM release), Pollok et al. (DF), and Chalupny et al. (W).

Schwarz et al. teach the polynucleotide sequence and deduced amino acid sequence of a receptor called "ILA" by the authors that is 99.8% identical at the amino acid level to SEQ ID NO:2 of the instant application, with a single conservative amino acid exchange at amino acid position 107 (K ->R, see attached "Sequence Comparison"). Because the instant claims only require that a portion or fragment of SEQ ID NO:2 of the instant application be used, the DNA of Schwarz et al. comprises the coding region of such a fragment. Schwarz et al. do not teach a soluble receptor polypeptide comprising the extracellular domain (ECD).

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Pollok et al. teach a plasmid comprising cDNA encoding the extracellular domain of mouse 4-1BB receptor polypeptide (4-1BBS, p. 772, col. 2, third paragraph). Also taught is expression and isolation of 4-1BBS by Western blot (rs-4-1BBP, p. 773, col. 1, third paragraph, and Fig. 1). This soluble polypeptide is taught as a pharmaceutical composition in admixture with a suitable carrier, *i.e.*, sodium phosphate buffer of pH 7.2, and was used to produce anti-4-1BB antibodies (p. 773, col. 1, last paragraph). An antibody so produced was useful for identification of 4-1BB on T-cells (p. 776, col. 1, second paragraph). Alkaline phosphatase conjugation to a secondary antibody is also described (p. 773, col. 2, second to last sentence of second paragraph, and p. 775, last paragraph).

Chalupny et al. teach a plasmid comprising cDNA encoding the extracellular domain of mouse 4-1BB receptor polypeptide linked in frame to human IgG1 (4-1BB Rg, p. 10369, col. 2, third ¶, and p. 10362, second ¶). The expressed fusion protein was soluble 4-1BB fused to human IgG, which was detectable by binding with anti-human IgG. Also taught is expression and isolation of 4-1BB Rg by affinity purification (Fig. 3). This soluble polypeptide is taught as a pharmaceutical composition in admixture with a suitable carrier, *i.e.*, PBS/Ca²⁺/Mg²⁺ (p. 10361 second ¶).

It would have been obvious to express the full-length or extracellular domain of the human polypeptide encoded by the cDNA of Schwarz et al. by substituting the full-length cDNA or portion of the cDNA of Schwarz et al. which corresponded to the ECD of the cDNA of Pollok et al. or Chalupny et al. to produce a soluble human 4-1BB polypeptide useful for the production of antibodies to aid in detection of cells expressing the receptor as taught by Pollok et al. with mouse T cells and by Chalupny et al. with extracellular matrix proteins. Further, it would have been obvious to substitute the human for the mouse soluble 4-1BB polypeptide in the pharmaceutical composition taught by Pollok et al. so that human specific antibodies could be made.

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Claims 5, 6, 24, 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alderson et al. (DH, Eur. J. Immunol, 1994, 24:2219-2227) and Kim et al. (DD, J. Immunol., 1993, 151: 1255-1262).

Alderson et al. teach a soluble H4-1BB polypeptide produced by transfecting a CD-
5 1/EBNA host cell with the expression vector pDC406 containing the entire extracellular domain of H4-1BB, which is a fragment of SEQ ID NO:2 of the instant application, and purifying the protein from culture on a G-Sepharose column (p. 2220, second paragraph). The entire ECD is from amino acid 1-186 of Figure 1 of Alderson et al, which is identical to the same region of SEQ ID NO:2 of the instant application. The ECD was produced fused to the Fc region of
10 human IgG1. Necessarily the DNA encoding this sequence would hybridize to one or more of SEQ ID NO:3-8 of the instant application as these are primers that hybridize to the naturally encoding sequence (see pages 15-16 of the instant application). Also taught is the H4-1BB ECD fusion protein in Freund's adjuvant, a pharmaceutically acceptable carrier. The full-length DNA was placed in the pDC410 expression vector (p. 2220, first paragraph, and p. 2221, col. 2, end of
15 first paragraph). An anti-human 4-1BB antibody was made which bound H4-1BB (p. 2220, fourth paragraph). Alderson et al. do not teach expression of full-length H4-1BB

Kim et al. teach expression of full-length murine 4-1BB in insect cells and HeLa cells (Figures 1c and 4c). Association of 4-1BB with p56^{lck} was tested by immunoprecipitation (p. 1259, col. 1), and the interaction of 4-1BB with CD4, CD8 and p56^{lck} theorized about
20 ("Discussion" section). "Whether 4-1BB regulates p56^{lck} activity and how their association can be influenced by extracellular stimulation is currently under investigation" (p. 1260, col. 2, 6 lines from bottom).

It would have been obvious to substitute the full-length human 4-1BB DNA of Alderson et al. for the full length 4-1BB DNA of Kim et al. and to express the encoded protein as taught
25 by Kim et al. for 4-1BB. It further would have been obvious to purify the complete human protein by the G-Sepharose method of Alderson et al. or the immunoprecipitation method of Kim et al., but using the anti-H4-1BB antibody of Alderson et al. instead of the anti-4-1BB antibody of Kim et al. One would have been motivated to express the full-length protein to determine if

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H4-1BB associated with p56^{lck} as 4-1BB did, and investigate how the two molecules are associated as suggested by Kim et al.

Prior Art

5 The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. The two references on the attached PTO-892 were supplied by Applicant in paper #23, however, no accompanying form 1449 could be found. As a result, these references are being made of record by the Examiner. They provide background information on the subject of TNF receptors.

10 ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

15 If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20 Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the
25 telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.



30 Patent Examiner, Art Unit 1646
August 23, 1999